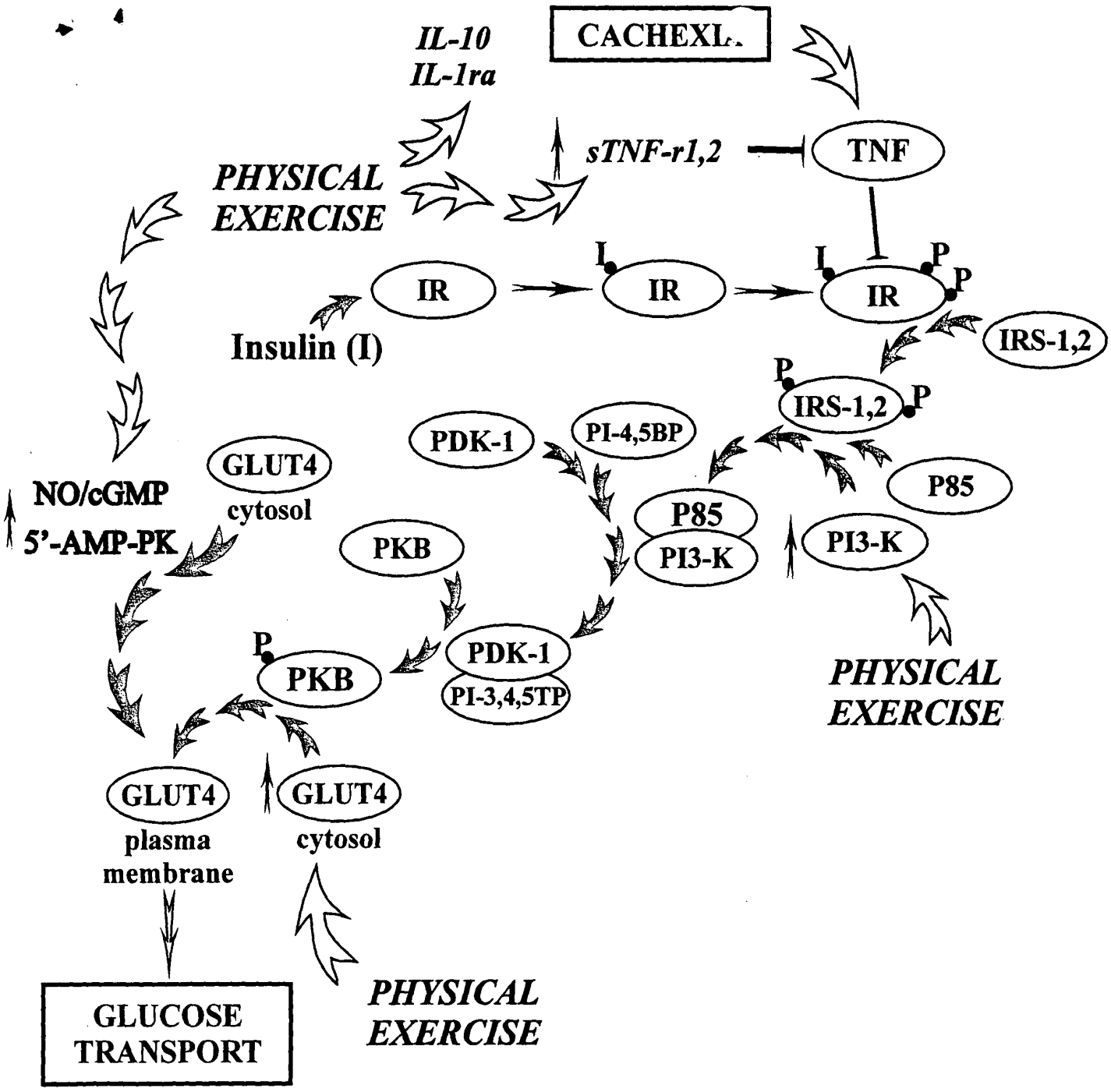

Figure 1. The effect of cachexia and physical exercise on the GLUT4 activation pathways.* Inflammation-induced TNF blocks activity of the insulin-activated IR. Physical exercise-suppression of the inflammatory responses (induced IL-10, IL-1ra, sTNF-r1,2) may block the synthesis/release of TNF thereby attenuating production of insulin-resistance. Activation of the GLUT4 pathways through enhanced NO, cGMP, 5'-AMP-PK activity, GLUT4 synthesis, PI-3 kinase activity, and GLUT4 translocation by physical exercise will enhance insulin sensitivity and possible prevent or reverse cachexia-associated insulin resistance.

*Because no single experiment has addressed all components of the illustrated molecular pathways, the interactions illustrated in Figures 1 through 4 are a composite of many in vivo and in vitro experiments involving many cell types (see text). These hypothetical constructs illustrate how exercise might be able to attenuate cancer- or cachexia-associated fatigue by activating GLUT4 translocation through non-insulin pathways, by enhancing PI3-K and GLUT4 synthesis, and by activating protein synthesis via Ca++- and ROS-mediated activation of the MAPK and JNK-MAPK pathways. Exercise also may decrease inflammatory responses through enhanced production of sTNF-r1, sTNF-r2, IL-10, and IL-1ra.

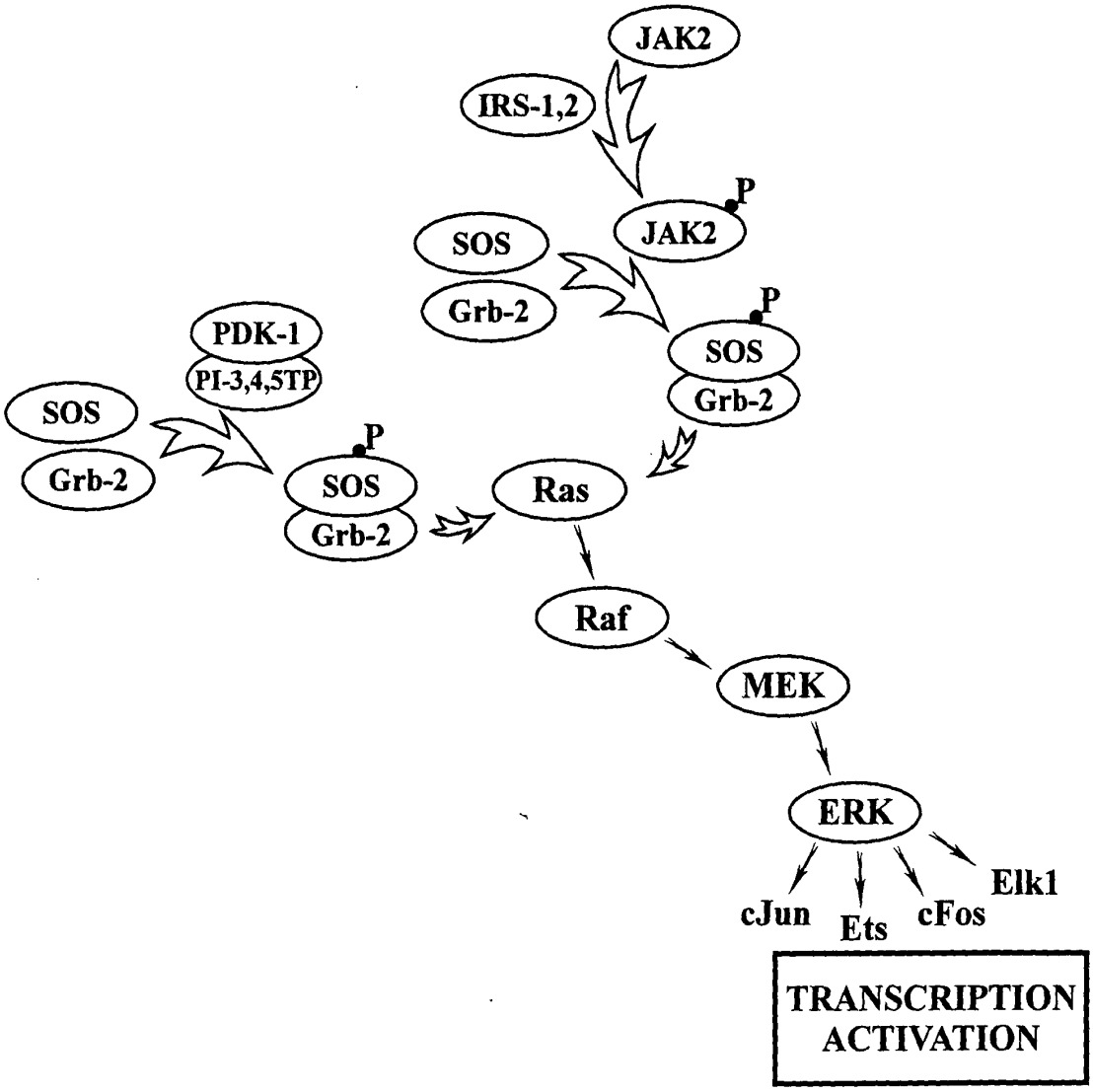

Figure 2. Insulin-mediated activation of the MAPK pathway of transcription activation. Both the activated IRS-1,2 (through activated JAK2) and the PDK-1:3,4,5TP complexes can activate the SOSGrb-2 complex which in turn activates ras of the MAPK pathway, resulting in enhanced protein synthesis.

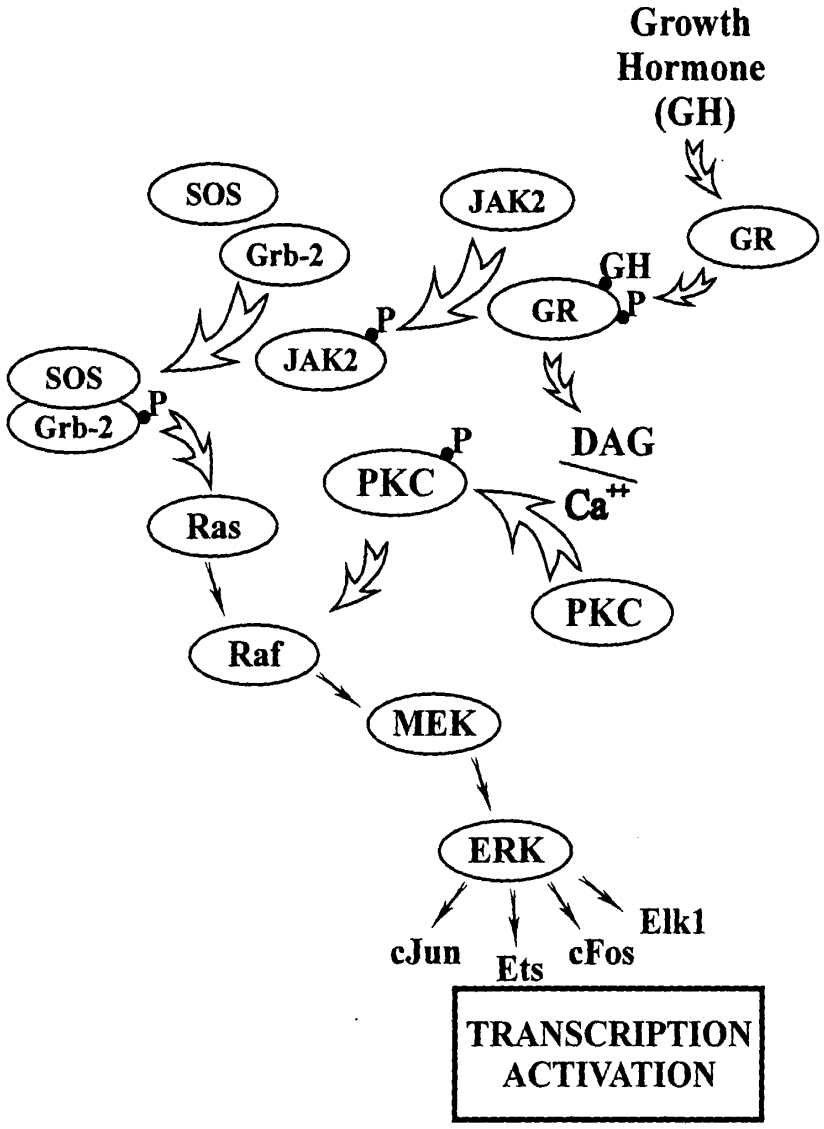

Figure 3. Growth-hormone (GH)–mediated activation of the MAPK pathway of transcription activation. The activated growth hormone receptor (GR) activates JAK2 which mediates the activation of ras via the SOSGrb-2 complex. Activated GR also stimulates the release of Ca^{++} into the cytosol (via DAG) which activates PKC. PKC in turn activates raf of the MAPK pathway; activation of both ras and raf results in enhanced protein synthesis.

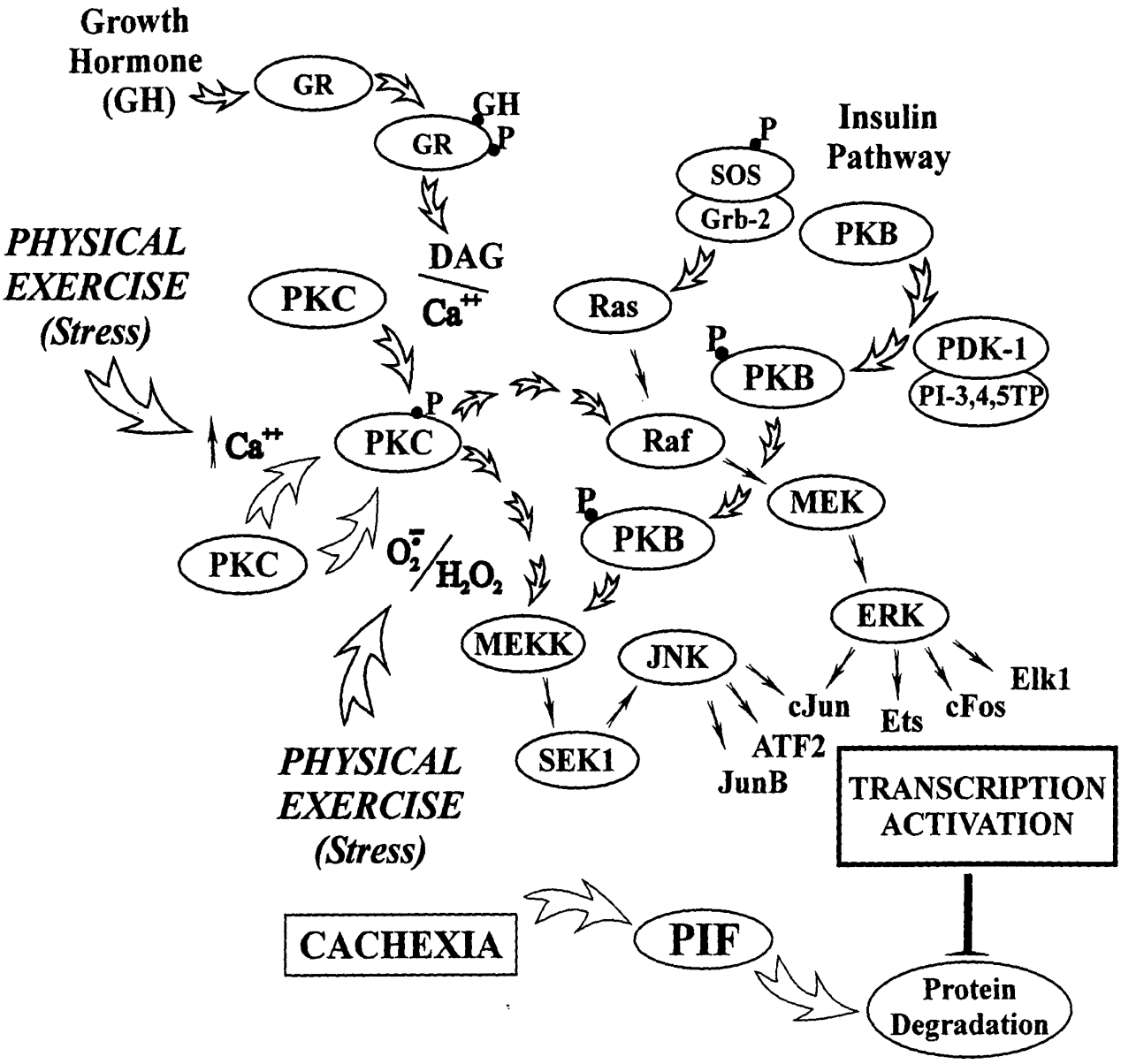

Figure 4. Interactive effects of physical exercise, insulin, and growth hormone on activation of the SAPK and MAPK pathways of transcription activation.
PKC is activated by physical exercise through enhanced Ca^{++} and ROS as well as by growth hormone through DAG/Ca^{++}. PKC in turn activates the SAPK and MAPK pathways by activating MEKK and raf, respectively. By enhancing insulin sensitivity and activating SAPK and MAPK independently if insulin and growth hormone, physical exercise should greatly enhance rates of protein synthesis beyond that expected by insulin or growth hormone alone; resulting in an attenuation of prevention of cachexia-associated muscle wasting and fatigue.

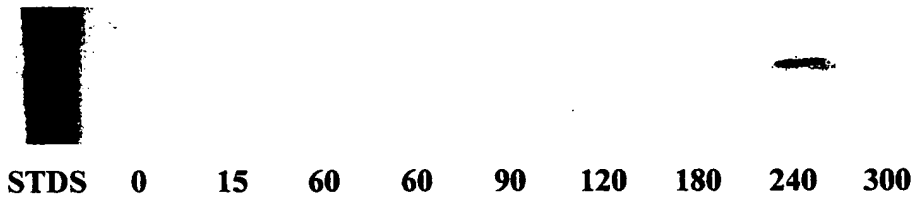

Figure 5. The effect of acute running exercise on Jun content of lung nuclei from rats.
Rats were exercised for 60 minutes and 3 rats killed at each time period of 0, 15, 30, 60, 90, 120, 180, 240, and 300 minutes from the start of the exercise. Lung nuclei were probed for jun using anti-cJun/AP-1 antibody in a western blot procedure. The blot was digitized, converted to grayscale, and the 35-45 kDa region of the blot which included the immunoreactive protein was then printed using an HP Photosmart 1215 printer at highest resolution.